Chapter

Cytopathology of Intraoral Salivary Gland Tumours and Tumour-Like Lesions: Diagnostic Challenges and Pitfalls

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Abstract

Fine needle aspiration cytology is an important diagnostic tool in cytopathology. There are many challenges and pitfalls encountered in intraoral salivary gland cytopathology as tumours of these glands show morphological diversity and overlapping features. There are often variable solid-cystic components, metaplastic or necrotic changes, fibrosis, hyalinisation and haemorrhage accounting for heterogeneity of these tumours. The tumour profile of intraoral salivary gland is quite different from the major salivary glands and needs special attention. A low-grade malignant tumour may sometimes mimic a benign neoplasm or a non-neoplastic lesion resulting in a false negative diagnosis. Moreover, misinterpretation and failure to recognize subtle morphological and architectural patterns of cells also pose diagnostic challenges. In this chapter, we intend to highlight the key cytopathological features of intraoral salivary gland tumours and tumour-like lesions with emphasis to overcome diagnostic challenges and pitfalls to avoid misdiagnosis which will aid in planning further management and treatment.

Keywords: Challenges, Cytopathology, Intraoral, Pitfalls, Salivary

1. Introduction

Fine needle aspiration cytology (FNAC) is an important diagnostic tool for initial evaluation of salivary gland (SG) tumours. The global annual incidence for all SG tumours varies from 0.4 to 13.5 cases per 100,000 population [1]. Tumours of intraoral salivary glands (SGs) are relatively uncommon as compared to tumours of major SGs and constitutes 10–15% of all SG tumours with relative frequency varying from 0.4% to 1.52% in different part of the world [2, 3]. These tumours have a very distinct profile from tumours of major SGs with reference to tumour histological type, clinical presentation and distribution. Majority of intraoral minor SG tumours are malignant in contrast to major SG tumours where benign tumours outnumber the malignant ones [4]. While some studies documents mucoepidermoid carcinoma (MEC) as the most common malignant tumour of minor SGs, other studies documents adenoid cystic carcinoma (ADCC) or pleomorphic adenoma (PA) as the most common tumour [5–10]. This difference in frequency of these histological types may be attributed to the differences in geographic location, race and varied

clinical presentation. The clinical presentation of intraoral SG tumours also range from mild pain to visible palpable mass in the oral cavity with or without ulceration leading to obstructive features such as difficulty in swallowing and deglutition. These tumours can occur at various intraoral locations such as mucosa of lips and cheeks, hard and soft palate, uvula, floor of the mouth, tongue, retromolar area and peritonsillar region. The hard palate is the most common site of occurrence [3–5]. Cytopathological evaluation of intraoral SG tumours is challenging as these tumours show heterogeneity and considerable morphological diversity and overlap [6]. The correct preoperative cytopathological diagnosis of intraoral SG tumours is essential for deciding further course of management and treatment. We here present key cytomorphological features of intraoral salivary gland tumours and tumour-like lesions with emphasis to overcome diagnostic challenges and pitfalls.

2. FNAC: a vital diagnostic tool in salivary gland pathology

FNAC is easy, minimally invasive, cost effective technique which provides a rapid initial preoperative diagnosis of SG tumours and has an impact on subsequent management and treatment [11]. The sensitivity and specificity of FNAC in diagnosing SG tumours is 85–100% and 90–100% respectively. The aspirated material obtained through FNAC can also be utilized for special staining such as Periodic acid-Schiff (PAS), Periodic acid-Schiff with diastase (PAS-D), Mucicarmine, Phosphotungstic acid-haematoxylin (PTAH), Acid fast bacilli (AFB) and Gram staining for further evaluation and diagnosis. PAS-D and mucicarmine are particularly useful for highlighting mucin containing cells in challenging cases of low-grade mucoepidermoid carcinoma (MEC). Similarly, PTAH stain can be applied on paraffin-embedded cell block preparation for identification oncocytic cells in challenging diagnosis of tumours with oncocytic differentiation. The cell blocks can also be utilized for Immunohistochemistry (IHC) for demonstrating epithelial and myoepithelial components in diagnosis of challenging tumours. The epithelial cells are positive for immunohistochemical markers such as cytokeratin and epithelial membrane antigen (EMA) and the myoepithelial cells show positivity for smooth muscle actin (SMA), calponin, p63 and S-100. Further, the aspirated material can also be used for microbiological culture, immunophenotyping and molecular analysis for confirming the cytological diagnosis. While the FNAC of palpable lesions in major SGs is relatively easy, the FNAC of intraoral SGs is challenging as many times aspirates are not cellular as these intraoral sites are often difficult to approach and sometimes inaccessible [10–12]. In such cases, radiological-guided FNAC may be advised for better yield of aspirates for subsequent cytological diagnosis. Also, while performing FNAC, there are chances of complications such as hemorrhage, nerve pain and damage and infection. There can be post FNAC induced changes in tissue such as squamous metaplastic changes, inflammation, granulation tissue formation and sometimes infarction, which may interfere with subsequent histological diagnosis. Therefore, familiarity with key cytological features with recognition of the subtle cytomorphological changes in cells is crucial for overcoming barriers and making a correct diagnosis.

3. The Milan system for reporting salivary gland cytopathology

The Milan system for reporting salivary gland cytopathology (MSRSGC) is an evidence based international classification and was developed by international consortium with the aim to standardize reporting terminology for categorizing SG lesions [13]. The intraoral SG tumour and tumour-like lesions can also be

categorized according to MSRSGC. The system has advantage and impact on clinical management of the patients [13, 14]. The system consists of following six broad diagnostic categories.

3.1 Category I: non-diagnostic

It includes FNAC smears with insufficient cellular material for making a definite diagnosis.

3.2 Category II: non-neoplastic

Includes FNAC smears with benign non-neoplastic lesions such as sialadenitis, sialolithiasis, granulomatous inflammation etc.

3.3 Category III: atypia of undetermined significance (AUS)

FNAC smears with limited cellular atypia that lacks qualitative or quantitative features of a neoplasm. Smears showing reactive or reparative atypia and metaplastic changes are included in this category.

3.4 Category IV

This category is classified into**:**

Category IVA: Benign Neoplasm – FNAC specimens showing characteristic cytomorphological features of a benign epithelial neoplasm.

Category IVB: Salivary Gland Neoplasm of Uncertain Malignant Potential (SUMP) – This category is most challenging as it includes FNAC specimens that have diagnostic feature of a neoplasm however, the possibility of malignant neoplasm cannot be excluded.

3.5 Category V: suspicious of malignancy

FNAC specimens that have some but not all the criteria for a specific diagnosis of malignancy and yet the overall cytologic features are sugsgestive of malignancy.

3.6 Category: VI malignant

FNAC specimens that are diagnostic of malignancy. The tumours of intraoral SGs with frank features of malignancy are included in this category.

4. Overview

In this chapter, the intraoral SG tumours and tumour-like lesions are being discussed under following six headings for better understanding of these tumours and related diagnostic challenges and pitfalls.

4.1 Matrix-containing tumours

The matrix producing tumours of intraoral SGs are pleomorphic adenoma (PA), adenoid cystic carcinoma (ADCC), polymorphous adenocarcinoma (POA). Carcinoma ex pleomorphic adenoma (CEPA), epithelial-myoepithelial carcinoma (EMC) are other matrix producing tumours that can also occur in intraoral SGs.

4.1.1 Pleomorphic adenoma (PA)

Pleomorphic adenoma is the most common benign tumour of SGs. Although, majority of PA occur in parotid gland, some studies documents PA as most common neoplasm in intraoral minor SGs [2, 4]. In the oral cavity, it usually presents as a solitary nodule or mass in the palate, sometimes with obstructive clinical symptoms.

Key cytological features – Smears show variable cellularity with cells arranged in clusters and sheets, embedded in a fibrillary chondromyxoid ground substance or matrix (**Figure 1**). The majority of cells are myoepithelial which may be ovoid, spindle, plasmacytoid, epithelioid, clear or stellate shaped. The nuclei of cells are round to oval, often with eccentric nucleus with bland finely granular chromatin and inconspicuous nucleoli. The cytoplasm is pale with well-defined cell borders. Stripped naked nuclei are not seen. PA may show diverse metaplastic changes including squamous metaplasia with or without keratinisation, oncocytic, clear cell, sebaceous, lipomatous and cartilaginous metaplasia. Hyaline globules can be seen. The prototypical PA is placed in benign category (IVA) of the Milan system.

Diagnostic challenges and pitfalls – Pleomorphic Adenoma (PA)

a. Sometimes, aspirate from PA may consist of only chondromyxoid substance without presence of epithelial and myoepithelial cells. The diagnosis of a neoplasm can be suspected but reaspiration is needed to rule out the possibility of other matrix producing tumours such as adenoid cystic carcinoma (ADCC) which can also occur at various intraoral locations. Both of these tumours have fibrillar metachromatic matrix and may show formation of hyaline globules. However, the matrix in PA is fibrillar with frayed edges (**Figure 2a**) while in ADCC the matrix is in form of beaded finger-like fragments, acellular spheres and tubules with sharply defined edges (**Figure 2b**) [15, 16]. Cellular PA with scant matrix particularly may resemble solid variant of ADCC. The cells of ADCC are basaloid and careful examination of nuclear chromatin of cells reveals distinguishing features. The cells in PA have bland finely granular chromatin while the cells of ADCC have coarse nuclear chromatin, high nuclear-cytoplasmic (N:C) ratio, scant cytoplasm and nucleoli [15]. The cells of ADCC may show focal nuclear moulding. Stripped naked nuclei can be seen in ADCC but not in PA. However, in challenging cases, it is not always possible to distinguish between the two entities. Such cases may be placed in SUMP category (IVB) of the Milan system. Follow-up and excision may be advised keeping clinical context in mind.

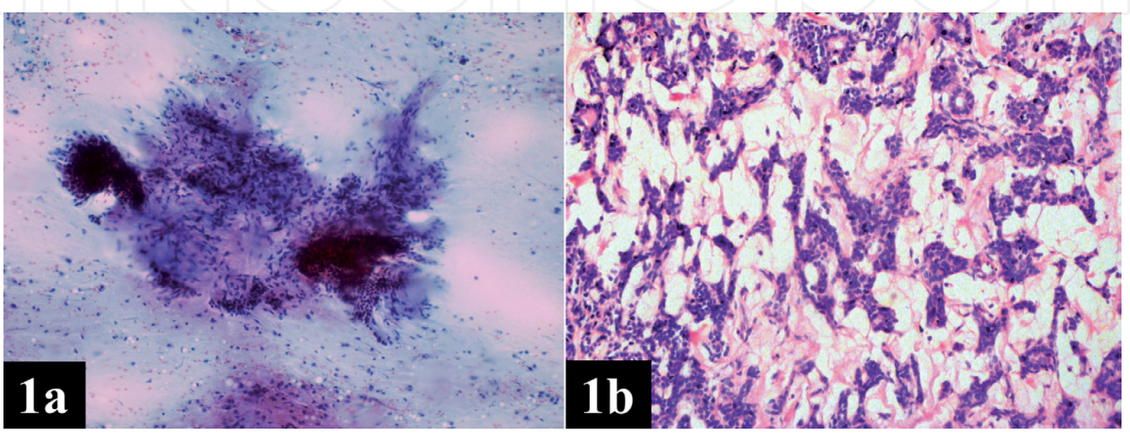

Figure 1.
1a: FNAC smear showing abundant chondromyxoid matrix with embedded cells in a case of pleomorphic adenoma (May-Grunwald Giemsa stain x 40), 1b: Corresponding histopathology showing nests, interlacing cords and strands of epithelial and myoepithelial cells in a myxoid stroma (Haematoxylin & Eosin x 40).

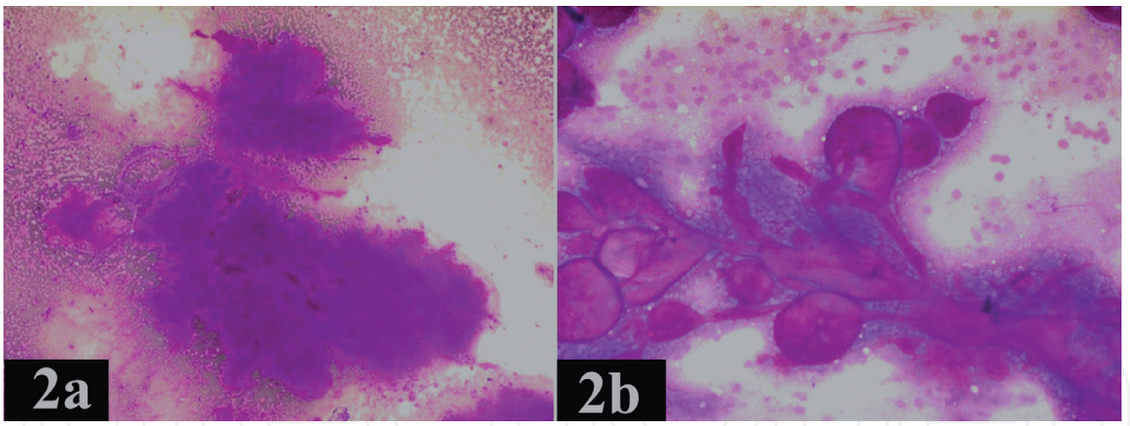

Figure 2.
2a: Smear showing abundant fibrillar metachromatic matrix with frayed edges in pleomorphic adenoma (May-Grunwald Giemsa stain x 40), 2b: Showing metachromatic matrix in form of acellular beaded, finger-like fragments and hyaline spherical globules with well-defined borders in a case of adenoid cystic carcinoma (May-Grunwald Giemsa stain x 40).

b. Cells in PA may undergo cystic and metaplastic changes. The aspirate may consist of metaplastic squamous cells with or without keratinisation (**Figure 3**) and scant or absent fibrillar metrachromatic matrix which can raise suspicion of a low-grade mucoepidermoid carcinoma (MEC) [16]. The intermediate cells of MEC in particular resemble squamous metaplastic cells of PA. However, the MEC usually have a dirty background and lacks myoepithelial cells, chondromyxoid material and keratinisation. One should also search for mucus cells, if MEC is suspected. In challenging cases, mucin containing cells of MEC can be demonstrated by using PAS-D or mucicarmine staining on cell blocks.

c. The myoepithelial cells in PA may sometimes show reactive atypia and prominent anisokaryosis which may sometimes be difficult to distinguish from malignant tumours [17]. Cells with reactive atypia can be recognized as they have bland chromatin and inconspicuous mitotic activity. The diagnostic pitfall is the occurrence of carcinoma ex-pleomorphic adenoma (CEPA). The development of CEPA in pre-existing intraoral PA is rare but few cases have been reported in literature [18]. History of long standing or recurrent PA in oral cavity with recent sudden increase in size along with cytological evidence

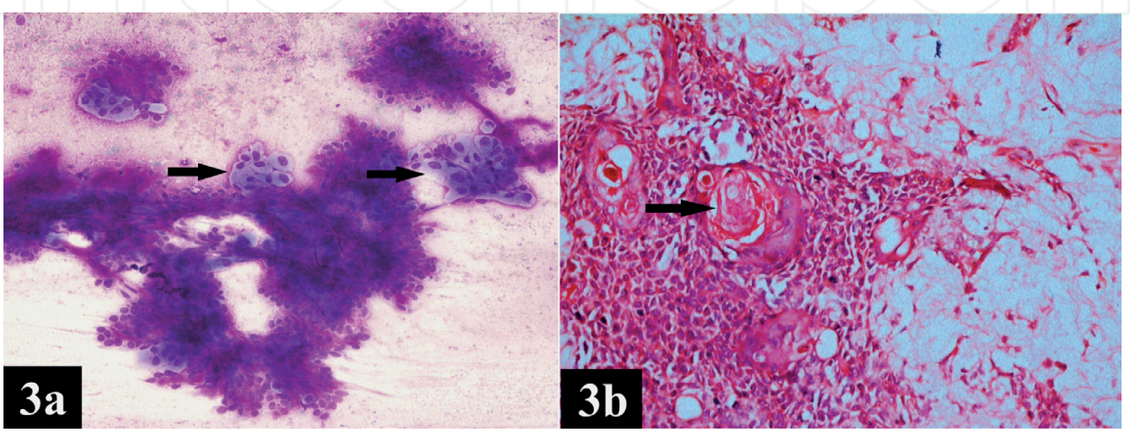

Figure 3.
3a: FNAC smear showing pleomorphic adenoma with squamous metaplasia (arrows) (May-Grunwald Giemsa stain x 4), 3b: Corresponding histology showing squamous metaplasia with evidence of keratinisation (arrow) surrounded by myxoid stroma (Haematoxylin & Eosin x 40).

of high grade atypical features in cells (**Figure 4**) and even a focal presence of areas depicting conventional PA consisting of benign cell clusters and chondromyxoid matrix (**Figure 4**), should lead to the diagnosis of CEPA [18, 19].

d. Epithelial-myoepithelial carcinoma (EMC) may sometimes also simulate a PA. It is a an unusual tumour and can also occur in minor SGs and palate [20]. This tumour can also have hyaline globules and show thin basement membrane-like metachromatic material around the clusters of cells. The predominant cell of EMC is myoepithelial. These cells are larger with abundant fragile clear delicate cytoplasm. Unlike PA, naked or stripped nuclei can be seen. Moreover, the biphasic population of epithelial and myoepithelial cells can be identified in EMC. The key cytological features and pitfalls of EMC are discussed at 4.3.1.

e. PA with predominant myoepithelial component (**Figure 5a**) may resemble other myoepithelial cell containing tumours such as myoepithelioma/myoepithelial adenoma (**Figure 5b**) in oral cavity. Myoepithelioma lacks chondroid stroma and duct cells seen of PA [21]. Distinction may not always be possible

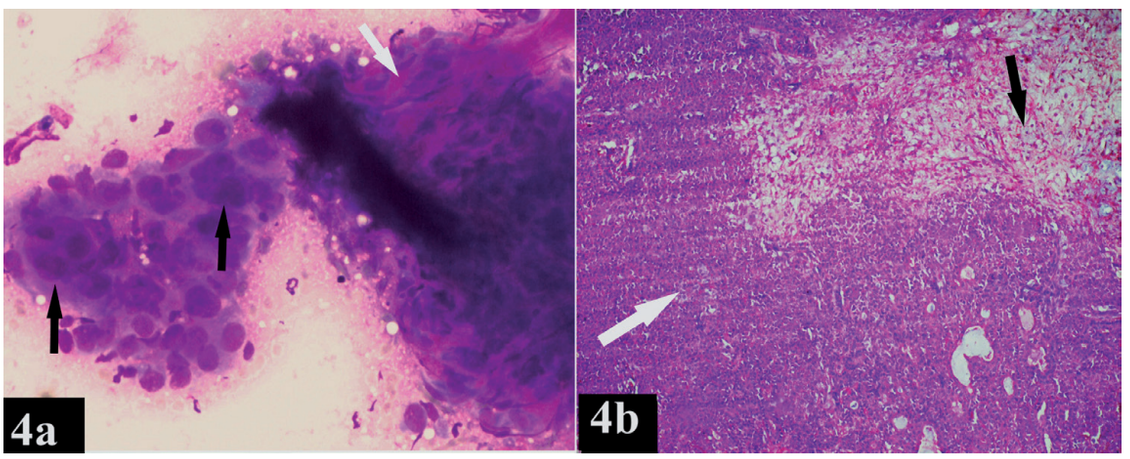

Figure 4.
4a: Showing malignant cells with high N:C ratio and hyperchromatic nuclei (black arrows) in a case of carcinoma ex-pleomorphic adenoma with evidence of metachromatic matrix of pre-existing pleomorphic adenoma (white arrow) (May-Grunwald Giemsa stain x 40), 4b: Corresponding histology showing sheet of malignant cells (white arrow) arising in background of myxoid stroma (black arrow) of pleomorphic adenoma (Haematoxylin & Eosin x 10).

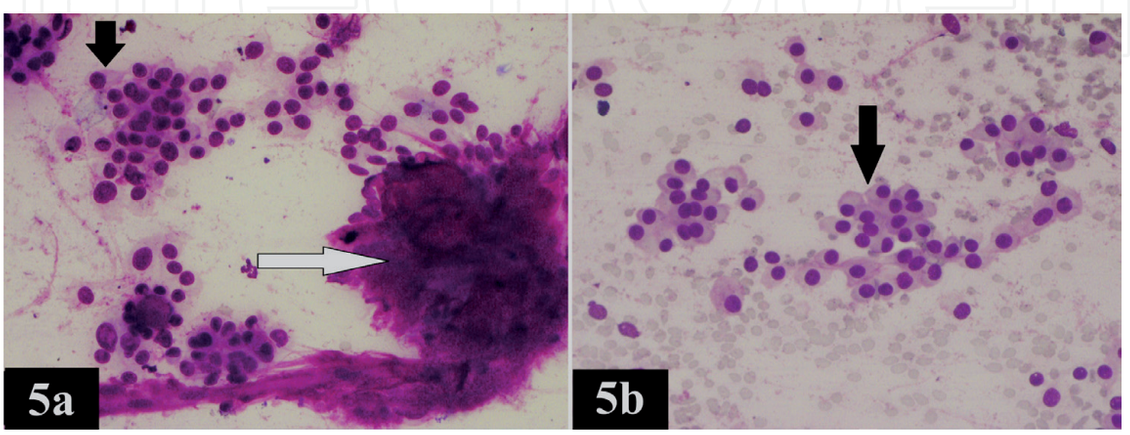

Figure 5.
5a: FNAC smear showing population of myoepithelial cells (black arrow) with metachromatic matrix (white arrow) in a case of myoepithelial predominant pleomorphic adenoma (May-Grunwald Giemsa stain x 40). 5b: Smear showing myoepithelial cells with pale to clear cytoplasm (arrow) in a case of a myoepithelioma (May-Grunwald Giemsa stain x 40).

and is not of much significance as both entities are benign (Milan system category IVA) and management is almost similar.

4.1.2 Adenoid cystic carcinoma (ADCC)

It constitutes nearly 10% of all SG tumours. Some studies suggest it to be the most common malignancy in minor salivary gland with hard palate being the most common site [22–24].

Key cytological features – Smears are cellular and cells are seen in clusters showing overlapping and multilayering. Tumour cells are also seen arranged in cup-shaped fragments and also scattered singly (**Figure 6**). The cells are basaloid with scant cytoplasm, round to ovoid hyperchromatic nuclei with coarse nuclear chromatin and nucleoli. The metachromatic matrix is in form of acellular beaded, finger like fragments, branching tubules and also forms hyaline spherical globules with well-defined borders (**Figure 2b**).

Diagnostic challenges and pitfalls – ***Adenoid Cystic Carcinoma (ADCC)***

a. PA and its distinguishing features from ADCC are discussed at 4.1.1a. However, the diagnosis of solid variant of ADCC is challenging as it lacks metachromatic matrix [25]. It can be distinguished from PA as it shows three dimensional clusters of basaloid cells with variable degree of pleomorphism. The cells are more hyperchromatic and angulated than in PA. In contrast to PA, mitosis, apoptosis and necrosis can also be seen [25]. IHC on cell blocks with CD -117 can be done in challenging cases which shows strong cytoplasmic positivity in ADCC [25, 26].

b. Sometimes, the basement membrane-like metachromatic material in EMC forms large globules resembling ADCC but the cellular compartment is entirely different in ADCC [26]. The cells of ADCC are basaloid with scant cytoplasm with round to ovoid hyperchromatic nuclei with coarse nuclear chromatin and nucleoli in contrast to myoepithelial cells of EMC with clear cytoplasm and round nuclei and vesicular chromatin [26].

c. Basal Cell Adenoma (BCA) can resemble ADCC. However, BCA arise predominantly in parotid and is extremely rare in the intraoral minor SGs [27]. It also shows metachromatic matrix and basement membrane like material and

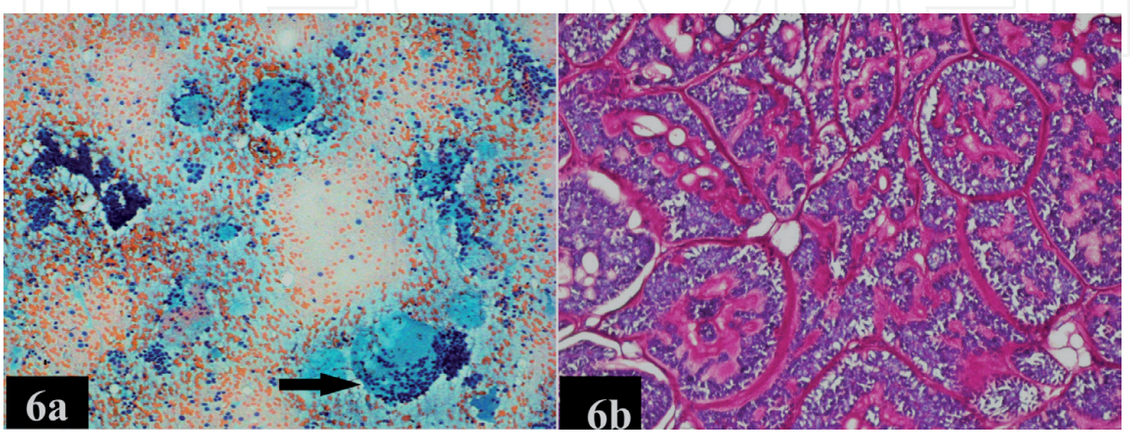

Figure 6.
6a: Smear showing large hyaline spherical globules with well-defined borders with attached tumour cells in cup-shaped fashion (arrow) and also scattered singly in a case of adenoid cystic carcinoma (Papanicolaou stain x 4). 6b: Corresponding histological section showing tumour cells surrounded by basement membrane-like metachromatic material (PAS x 40).

basaloid cells similar to ADCC but cells have granular chromatin rather than coarse nuclear chromatin seen in ADCC. The cells occasionally show peripheral palisading. Squamous morules or metaplasia can be frequently seen in BCA but not in ADCC.

d. Canalicular (CA) /Ductal Adenoma occurs in oral cavity predominantly in upper lip and buccal region [28]. It has overlapping cytological features with BCA. Cells of CA are cuboidal to columnar and are seen in clusters and cords. Unlike ADCC, the cells are monomorphic with finely dispersed chromatin and inconspicuous nucleoli.

4.1.3 Polymorphous adenocarcinoma (POA)

Previously called as polymorphous low grade adenocarcinoma, it is a low-grade matrix containing tumour occurring predominantly in intraoral minor salivary gland with palate being the most common site [29].

Key cytological features – Cells are seen in clusters, papillae, trabeculae, singly scattered and also in form of epithelial fragments attached to fibrovascular stromal cores (**Figure 7**). The cells are monomorphic with oval nuclei, open chromatin and indistinct nucleoli with moderate amount of cytoplasm. Small hyaline globules can be seen admixed with these cells.

Diagnostic challenges and pitfalls – Polymorphous Adenocarcinoma (POA).

The cytological features of POA may resemble PA or ADCC [30]. The matrix of POA may be fibrillar and myxoid resembling a PA or can form hyaline globules similar to ADCC. However, the papillary architecture of cells is found in POA and its presence can distinguish it from PA and ADCC. The cells of ADCC are basaloid with coarse nuclear features rather than fine open nuclear features seen in POA [30].

4.2 Cystic tumours

Cystic tumours of intraoral SGs range from benign tumours such as sclerosing polycystic adenosis, cystadenoma, cystic PA, duct papilloma to malignant tumours such as low-grade MEC and papillary cystic variant of acinic cell carcinoma (AciCC). Evaluation and interpretation of these cystic tumours is particularly challenging as usually the aspirate of these tumours is hypocellular. This may result in false negative diagnosis particularly in a low-grade malignant cystic tumours.

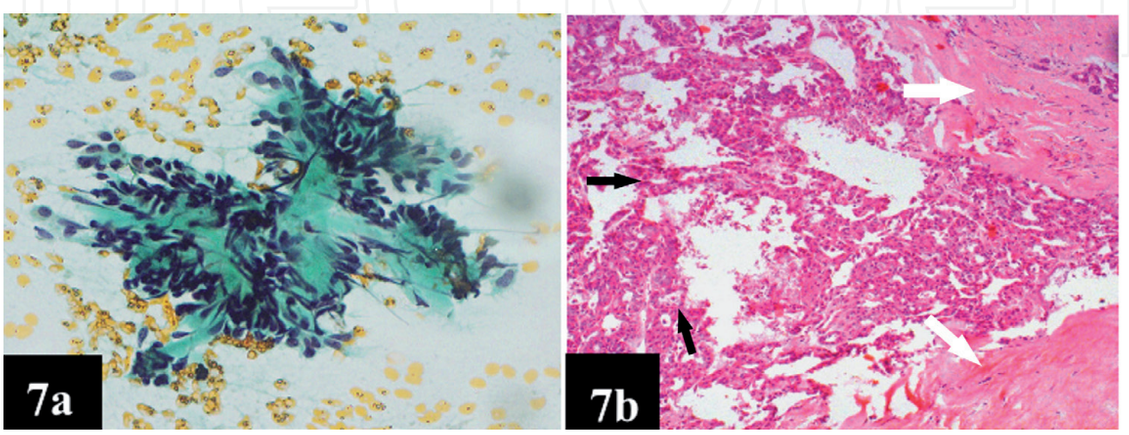

Figure 7.
7a: Smear showing monomorphic small round to oval epithelial cells attached to fibrous stromal core in a case of polymorphous adenocarcinoma (Papanicolaou stain x 40), 7b: Corresponding histology showing growth of tumour cells in glandular and acinar pattern (black arrows) surrounded by adjacent fibrous stroma (white arrows) (Haematoxylin & Eosin x 10).

Diagnostic challenges and Pitfalls – Cystic Tumours

a. **Sclerosing polycystic adenosis (SPA)** is a rare benign tumour reported in intraoral minor SGs [31]. It is predominantly cystic and shares common features with fibrocystic disease and sclerosing adenosis of the breast. The key cytological features include epithelial cells in syncytial sheets with apocrine changes with variable granular to oncocytic and vacuolated cytoplasm in a cystic background consisting of foamy histiocytes and proteinaceous material. SPA is frequently associated with intraductal proliferations. Ductal cells of SPA with vacuolated cytoplasm can resemble cells of AciCC or a low-grade cystic MEC. However, the apocrine metaplastic changes in cells is the key feature which in proper clinical context of long history of benign tumour favours a diagnosis of SPA over other carcinomas [31].

b. **Cystadenoma** is also a rare benign tumour occurring in minor SGs [32]. The tumour is multicystic and cytology reveals cuboidal to columnar cells in clusters and papillae with bland nuclear features and oncocytic cytoplasm. The cytoplasm of cells may sometimes become epidermoid and may resemble cells of low-grade MEC. Cystadenoma is indistinguishable from cystadenomacarcinoma on cytology. Histological evidence of invasion is required for diagnosis of cystadenocarcinoma [32].

c. **Duct papilloma (DP)** is a benign tumour arising predominantly from the ducts of minor SGs and characterized by intraductal proliferation of cells in form of broad papillary projections [33]. It is composed of epidermoid cells and mucous cells and can resemble a MEC. However, the papillary architecture of DP can help to distinguish it from MEC.

d. **Mucoepidermoid carcinoma (MEC)** – It is the most common malignancy of intraoral SGs in young adults and children [7–9]. Palate is the most common site of occurrence. It is composed of mucin containing cells, intermediate cells and epidermoid/squamous cells. The low-grade MEC is cystic and particularly challenging as it mimics other cystic neoplasms and non-neoplastic cystic tumour-like lesions [34]. Aspirates from low-grade MEC show mucin containing vacuolated cells in a predominantly cystic background with debris. However, it can be recognized by presence of at least few or occasional cluster or single intermediate or epidermoid cells (**Figure 8**). Intermediate

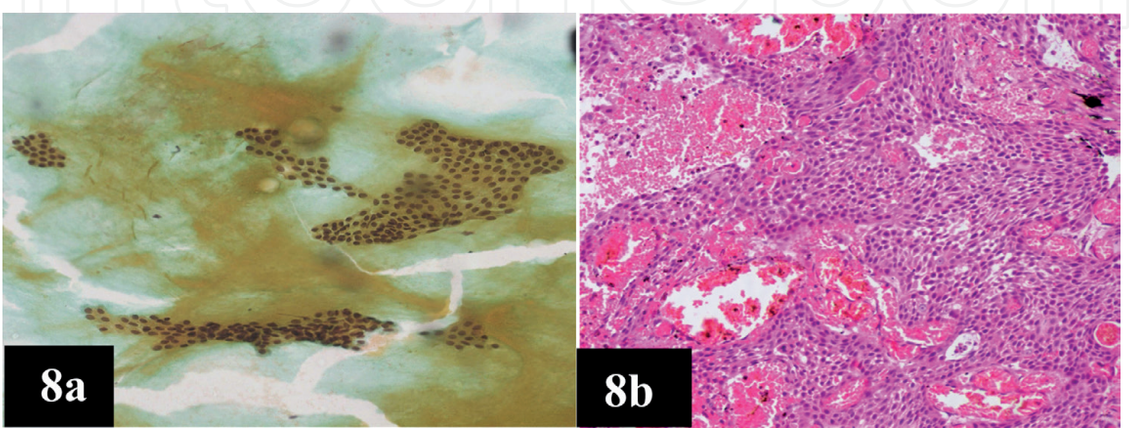

Figure 8.
8a: Showing small sheets and clusters of epidermoid cells in a cystic mucoid background in a case of low-grade mucoepidermoid carcinoma (Papanicolaou stain x 10), 8b: Corresponding histology showing sheets of epidermoid cells (Haematoxylin & Eosin x 10).

cells appear like a metaplastic squamous cell. Mucin filled cells can also be demonstrated by using mucicarmine staining on cell blocks. Sometimes, epithelial cells are not aspirated and aspirate consist of only mucoid material with few histiocytes and muciphages resembling a mucocele [35]. In proper clinical contexts, such cases should be reported with differential diagnosis of low-grade MEC and must be followed-up. High-grade MEC is predominantly solid but can have a cystic component. Smears from a high-grade MEC are cellular and are readily recognisable and shows three-dimensional clusters and sheets of atypical cells with malignant squamoid features. The cells are polygonal and have a high N:C ratio with hyperchromatic nuclei often with a prominent nucleolus. If a high-grade MEC is suspected, search should be done for mucin containing vacuolated cells. Moreover, keratinsation is not the feature of MEC which can aid in distinguishing MEC from metastatic squamous cell carcinoma [35].

e. **Cystic pleomorphic adenoma (PA)** may sometimes mimic a low-grade MEC [35]. However, identification of even a focal metachromatic fibrillary material gives clues to the diagnosis. The differentiating features of PA from MEC are discussed at 4.1.1b.

f. **Papillary cystic variant of AciCC** is another important differential in cystic SG tumours [36]. It is distinguished from other low-grade carcinomas as it shows polygonal cells with fine, abundant, delicate and vacuolated cytoplasm similar to conventional AciCC but arranged in a predominant papillary pattern consisting of a cells attached to a capillary meshwork or around a fibrovascular core (**Figure 9**) [36]. The background is cystic and can show presence of lympho-histiocytes.

4.3 Tumours with clear cell and vacuolated cell pattern

The differential diagnosis of tumours of intraoral SGs comprising of clear cells and vacuolated cell pattern include – Epithelial–Myoepithelial carcinoma (EMC), Myoepithelial tumours such as myoepithelioma (ME) and myoepithelial carcinoma (MC), clear cell carcinoma (CCC), mucoepidermoid carcinoma (MEC), acinic cell carcinoma (AciCC), secretory carcinoma (SC).

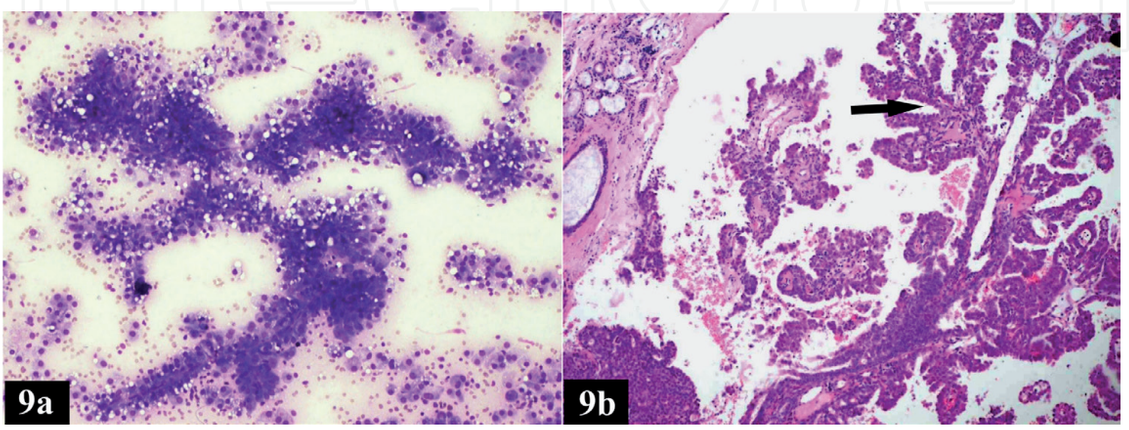

Figure 9.
9a: Showing cells arranged in a predominant papillary architecture with fine fibrovascular core in a case of acinic cell carcinoma. The cells have fine vacuolated cytoplasm (May-Grunwald Giemsa stain x 4), 9b: Corresponding histology showing branching papillae (arrow) with fibrovascular core (Haematoxylin & Eosin x 4).

4.3.1 Epithelial–myoepithelial carcinoma (EMC)

It is a an unusual tumour of major salivary gland predominantly occurring in parotid (60–80%) but can also be seen in minor SGS [20]. Palate is the most common site of occurrence and clinical presentation can be a ulcerative nodular lesion.

Key cytological features – The smears are cellular comprising of biphasic population of epithelial and myoepithelial cells. The myoepithelial cells are seen in loosly cohesive sheets, clusters and spheres with fragile, pale to clear delicate glycogen rich cytoplasm that disperses in background resulting in many naked or stripped nuclei. The nucleus of myoepithelial cells is round to oval with open chromatin and small distinct nucleoli (**Figure 10a**). Epithelial cells are seen usually in tight cohesive clusters. Sometimes mild nuclear atypia can be encountered. Hyaline stromal globules and basement membrane-like material can also be seen. The biphasic pattern of EMC can be demonstrated by using IHC on cell blocks with low molecular weight keratin and epithelial membrane antigen (EMA) for highlighting the duct cells and with smooth muscle actin (SMA), calponin, p63 and S-100 for highlighting the myoepithelial cells component [37]. Points of differentiation of EMC with other tumours with clear and vacuolated cells are discussed with each individual tumour.

4.3.2 Myoepithelioma (ME)

Myoepithelioma (ME) is a benign tumour that can occur in minor SGs with palate being the most common site. The myoepithelial cells in ME have pale to clear cytoplasm (**Figure 5b**), resembling myoepithelial cells of EMC. However, the myoepithelial cells of EMC are larger than that of ME due to presence of abundant glycogen [21]. Also, ME lacks the biphasic pattern of EMC (**Figure 10a**). ME may undergo transformation into myoepithelial carcinoma (MC). However, atypical cytological features such as nuclear pleomorphism, coarse chromatin with prominent nucleoli with background necrosis and mitotic activity seen in MC can differentiate between the two [21]. Differentiation of ME from cellular PA with predominant myoepithelial component is already discussed at 4.1.1e.

4.3.3 Clear cell carcinoma (CCC)

Clear cell carcinoma (CCC) of the SG is a rare low-grade malignancy that occurs primarily in intraoral minor salivary glands predominantly in the palate [38].

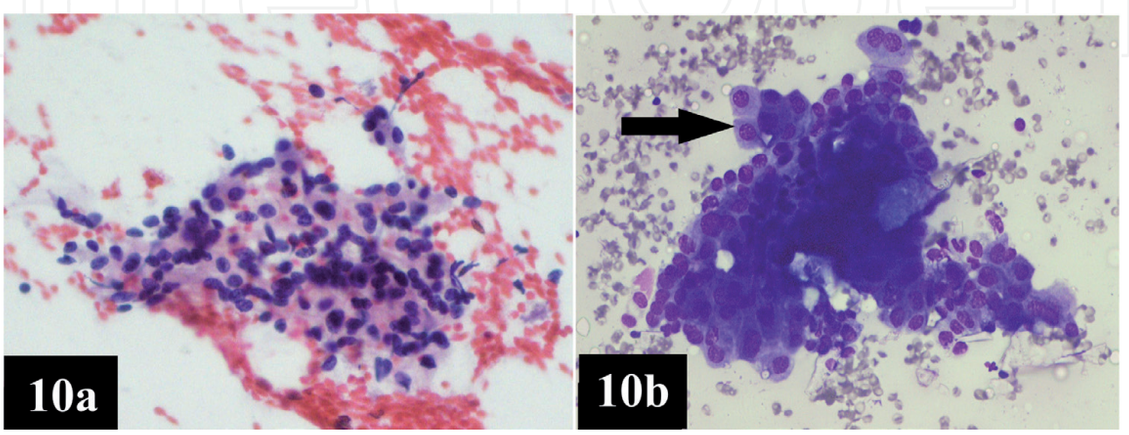

Figure 10.
10a: Smear showing admixture of dual population of cells comprising of epithelial and myoepithelial cells in a case of epithelial myoepithelial carcinoma (Haematoxylin & Eosin x 40), 10b:s Smear showing a cluster of cells with multilayering of round to polygonal oncocytic cells (arrow) with round nucleus and abundant dense granular cytoplasm in a case of an oncocytoma (May-Grunwald Giemsa stain x 40)

Epithelial cells of CCC are seen in clusters and sheets with prominent cell borders, uniform round to ovoid nuclei, granular chromatin and abundant glycogen rich clear cytoplasm**.** The cells of **CCC** may resemble myoepithelial cells of EMC. Unlike EMC, CCC lack evidence of either ductal or myoepithelial differentiation.

Clear cells can be encountered in MEC of minor SGs. However, identification of other accompanying cells (intermediate and epidermoid cells) in MEC gives clues to the diagnosis [34]. Mucin in cells of MEC can also be demonstrated by mucicarmine stain on cell blocks.

4.3.4 Acinic cell carcinoma (AciCC)

It is a low-grade tumour having predominantly vacuolated cell morphology. AciCC predominantly occurs in parotid (75–90%) and the remaining cases occur in intraoral minor salivary glands predominantly in buccal mucosa [39].

Key cytological features – Smears are cellular and consist of cells in three-dimensional clusters, sheets, micro-acinar groups and papillae with scant inconspicuous fibrovascular stroma. The cells are large with abundant fragile vacuolated basophilic to eosinophilic cytoplasm [40]. The nuclei are round, uniform with bland chromatin. Sometimes, the cells show oncocytic or clear cell changes. The background is clean with presence of bare stripped nuclei. The papillary cystic variant also has cells similar to conventional AciCC but the cells are arranged in a predominant papillary pattern with cells attached to a capillary meshwork or around a fibrovascular core (**Figure 9**). The cytoplasmic zymogen granules in AciCC can be demonstrated by PAS-D stain. Recent studies of IHC on cell blocks with DOG 1 reveals strong diffuse granular cytoplasmic positivity in AciCC [41].

Diagnostic challenges and pitfalls – Acinic Cell Carcinoma (AciCC)

a. Sometimes, aspirates from non-neoplastic SG tissue may resemble cells of AciCC. Single stripped nucleus of non-neoplastic SG may be difficult to distinguish from AciCC. However, cell groups and clusters of AciCC can be identified as they show three dimensional architecture with overlapping unlike the regularly arranged acini attached to duct with a thin fibrovascular core in a normal non-neoplastic SG tissue [40].

b. Sebaceous adenoma (SA) and sebaceous lymphadenoma are benign tumours and can occur in minor SGs and also have cells with vacuolated to clear cytoplasm [42]. Similarly, sebaceous carcinoma may arise rarely in intraoral SGs. The cells of these tumours contain cytoplasmic fat which can be demonstrated by oil-red O staining. PAS-D staining is negative for zymogen granules as seen in AciCC.

c. Cells of AciCC may show oncocyte like changes and sometimes resemble an oncocytoma**.** However, the typical cells of AciCC with finely vacuolated delicate cytoplasm can be identified. Many stripped or bare nuclei are also seen which are absent in oncocytoma [40]. Cell block preparation can be used to demonstrate periodic acid Schiff with diastase (PAS-D) positive zymogen granules in AciCC. Also, if oncocytoma is suspected, then phosphotungstic acid-haematoxylin (PTAH) stain can be done on cell blocks which shows strong positive cytoplasmic staining due to presence of abundant mitochondria.

d. AciCC may show clear cells which may resemble other tumours with clear cells such as EMC. The biphasic population of myoepithelial and epithelial cell can identified in EMC. The key cytological features of EMC are discussed at 4.3.1.

4.3.5 Secretory carcinoma (SC)

Previously called as mammary analogue secretory carcinoma, it is a new subtype of SG carcinoma and is reported to occur in minor salivary gland [43]. It also shows cells with vacuolated to clear cytoplasm.

Key cytological features – Aspirates show loosely cohesive epithelial cells arranged in small sheets, papillary fragments, acinar groups or follicular structures and also dispersed singly. The cells show variable cytoplasm ranging from granular to vacuolated and eosinophilic to clear cytoplasm. The cells show minimal or no pleomorphism. Background shows mucinous material.

Diagnostic challenges and pitfalls – The vacuolated cells may resemble cells of AciCC but lack intracytoplamic zymogen granules. Also, IHC on cell blocks is positive for markers such as mammaglobin, S-100 and vimentin and negative for DOG1 [41, 43].

4.4 Oncocytic tumours

4.4.1 Oncocytoma

Oncocytoma is a benign tumours of SG predominantly occurring in parotid. However, these tumours are also known to occur in intraoral minor SGs [44].

Key cytological features – The cells are seen in two or three dimensional and multilayered clusters. The cells are round to polygonal with oncocytic morphology consisting of dense granular abundant cytoplasm with a round nucleus and distinct nucleolus (**Figure 10b**). The background is clean without debris, fluid and lymphocytes. The oncocytic cytoplasm of cells containing abundant mitochondria can be highlighted by strong positivity for phosphotungstic acid-haematoxylin (PTAH) stain.

Diagnostic challenges and pitfalls – Oncocytic Tumours

a. The presence of oncocytes can be seen in other tumours of SGs particularly acinic cell carcinoma (AciCC) and less commonly in mucoepidermoid carcinoma (MEC) [40, 45, 46]. The distinguishing features of oncocytoma from AciCC are discussed at 4.3.5c.

b. Intraoral PA may also undergo metaplastic oncocytic change through a process known as oncocytosis. Oncocytosis is characterized by metaplastic change in SGs. Sometimes, entire salivary gland parenchyma is replaced by oncocytes mimicking an oncocytoma [45, 46]. But the typical metachromatic fibrillary matrix can usually be identified after adequate sampling in PA.

c. Oncocytic variant of mucoepidermoid carcinoma (OMEC) is a low-grade tumour and may resemble an oncocytoma as it shows bland oncocytic cells with minimal nuclear atypia [47]. However, it shows characteristic mucinous goblet cells of MEC. Also, epidermoid and intermediate cells should always be searched upon, if OMEC is suspected. Cell block can also be used to confirm mucin in goblet cells by mucicarmine staining.

d. Oncocytic carcinoma is a rare aggressive carcinoma and may develop in pre-existing oncocytoma. However, it can be distinguished from oncocytoma as it shows atypical oncocytic cells with nuclear pleomorphism. Mitosis and necrosis can also be seen.

e. Warthin's Tumour constitutes 5–15% of all salivary gland tumours. Although, it shows cohesive two or three- dimensional clusters of oncocytic cells resembling an oncocytoma but it occurs almost exclusively within the parotid gland [46]. The background is usually cystic with debris, lymphocytes and lympho-histiocytes.

4.5 Other carcinoma of intraoral salivary glands

4.5.1 Adenocarcinoma not otherwise specified (NOS)

It is an aggressive invasive tumour showing features that are not specific for any particular tumour type. It is a usually a diagnosis of exclusion. It constitutes 10–15% of all SG tumours and about 40% cases are reported in minor salivary glands with palate being the most common site [48].

Key cytological features – It shows glandular or ductal differentiation but patterns and cellular features are non-specific. The cells may be seen in nests, tubules, clusters or cords. The cellular features are variable and range from subtle low-grade tumours to a high-grade carcinoma.

Other SG carcinomas such as salivary duct carcinomas, intraductal carcinoma, lymphoepithelial carcinoma, primary squamous cell carcinoma and carcinosarcomas are rare and are reported to occur in major salivary gland and not in intraoral minor SGs.

4.6 Tumour-like lesions of intraoral salivary glands

4.6.1 Mucocele

Amongst non-neoplastic lesions, mucocele or mucous retention cyst occur in intraoral SGs and can mimic a low-grade cystic tumour. Mucocele is a pseudocyst which lack epithelial lining and contain extravasated mucin. These usually develops in minor SGs particularly on the lips and other sites such as tongue [49]. FNAC smears from mucocele are hypocellular with histiocytes and muciphages in an abundant mucoid background**.** Few giant cells can also be seen. Cystic consistency and mucoid background with muciphages may raise a possibility of low-grade MEC but other features of MEC such as intermediate and epidermoid cells are absent.

4.6.2 Sialadenosis (SA)

Sialadenosis (SA) is non-inflammatory and non-neoplastic enlargement of SGs predominantly occurring in parotid. However, it is also documented to occur in minor SGs in few reports in literature [50]. Aspirates from SA show plenty of acinar cells with hypertrophic changes. Sometimes, the cells may resemble cells of AciCC but in SA the architecture of normal SG tissue is maintained with regularly arranged acini instead of overlapping three-dimensional clusters, groups and sheets of acini in AciCC.

4.6.3 Sialadenitis

Inflammation of SGs may result from various causes but predominantly it occurs due to stenosis or obstruction of SG ducts because of sialolithiasis, trauma or secondary involvement by tumours [51, 52]. It may present with swelling and sometimes mimic a neoplasm.

4.6.4 Acute sialadenitis (AS)

Acute sialadenitis (AS) is usually a bacterial inflammation of the SGs and usually affects the parotid. However, it may also affect minor SGs [52]. Aspirates from AS usually shows abundant neutrophils, macrophages, few duct cells with reactive changes in a degenerating background. Sometimes, AS may occur as a part of underlying tumour. Non-regressive swelling on antibiotic treatment with abundant obscuring inflammation showing even focal evidence tumour such as chondromyxoid material or mucin laden or keratinized cells, should raise suspicion of a underlying hidden tumour and need to be followed-up by reaspiration or biopsy.

4.6.5 Chronic sialdenitis (CS)

Chronic sialdenitis (CS) can also affect minor SGs [53]. It may occur due to repeated episodes of inflammation or secondary to treatment such as radiation therapy for other cancers. Aspirates from CS are hypocellular and shows few clusters of duct cells, fragments of fibrous tissue in background showing lymphocytes. Acinar cells are usually not seen and are absent. The duct cells may undergo metaplastic squamous changes and may show reactive atypia, raising possibility of MEC. In such cases, other features of MEC like mucinous cells and frank epidermoid cells and dirty mucoid background give clues to the diagnosis. Frank atypical features of a carcinomatous cells such as hyperchromatic nuclei and high N:C ratio can be differentiated from reactive changes due to either chronic infection or treatment.

4.6.6 Granulomatous sialadenitis (GS)

Granulomatous sialadenitis (GS) can present clinically as a slow-growing mass that can mimic a neoplasm. Aspirates are usually hypocellular and consist of clusters of epithelioid histiocytes, multinucleated giant cells, lymphocytes and duct cells. Transforming or ill-formed epithelioid cells should not be mistaken for an epithelial neoplasm.

4.6.7 Lymphoepithelial sialadenitis (LESA)

Lymphoepithelial sialadenitis (LESA) primarily affects salivary and lacrimal glands and is also reported in minor SGS [54]. It is believed to be an autoimmune disorder and is associated with sjogrens syndrome and other connective tissue disorders. Aspirate shows lymphoepithelial complex comprising of clusters of cohesive duct cells infiltrated by lymphoid cells. The duct cells may show metaplastic squamous changes or reactive atypia. The background consist of abundant population of large and small lymphoid cells in various stages of maturation, plasma cells and tingible body macrophages. LESA is associated with increased risk of lymphoma particularly extranodal marginal zone lymphoma of MALT type and sometimes it is indistinguishable from it [55]. Ancillary tests such as IHC on cell blocks and immunophenotyping with flow cytometry should be done to distinguish between LESA and lymphoma. Reactive lymphnode can mimic LESA but lymphoepithelial complex is absent. Since LESA can be cystic, other pitfall includes cystic tumours showing background of lymphocytes such as AciCC and low-grade MEC which can be differentiated by presence of their other cytological features.

5. Conclusions

FNAC of intraoral SGs is challenging. There are many diagnostic challenges encountered in cytopathology of SG tumours as these tumours show morphological diversity and overlapping features with other neoplastic and non-neoplastic lesions. Careful assessment of morphological features with acquaintance of diagnostic challenges and pitfalls not only aid in avoiding misdiagnosis but also aid in planning further management and treatment.

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Conflict of interest

The authors declare no conflict of interest for this chapter.

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